IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Michael Tyo et al.	Art Unit	: 1633
Serial No.	: 10/758,970	Examiner	: Ileana Popa
Filed	: January 16, 2004	Conf. No.	: 6224
Title	: CONTINUOUS-FLOW METHOD FOR PREPARING MICROPARTICLES		

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BRIEF ON APPEAL

Appellant is appealing the final rejection of claims 1-55 in the Final Office Action dated December 26, 2008. A Pre-Appeal Brief Request for Review and a Notice of Appeal were filed on June 18, 2009, and received by the U.S. Patent and Trademark Office on that date. A Notice of Panel Decision from Pre-Appeal Brief Review was mailed on July 20, 2009, indicating that the application will proceed to the Board of Patent Appeals and Interferences.

(i) Real Party in Interest

The Real Party in Interest is Eisai Inc., the assignee of record.

(ii) Related Appeals and Interferences

There are no prior or pending related appeals, judicial proceedings, or interferences.

(iii) Status of Claims

Claims 1-55 are rejected and under appeal.

(iv) Status of Amendments

All previously filed amendments have been entered. No amendments were made subsequent to the final rejection.

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(v) Summary of Claimed Subject Matter

Claim 1, the only independent claim under appeal, is directed to a scalable continuous process for preparing nucleic acid-containing microparticles and contains the following steps: (a) providing a mixing chamber and a solvent removal device; (b) continuously supplying a first emulsion to a mixing chamber; (c) continuously supplying a second aqueous solution to the mixing chamber; (d) continuously emulsifying the first emulsion and the second aqueous solution in the mixing chamber to form a second emulsion; (e) continuously transferring the second emulsion from the mixing chamber to a solvent removal device; and (f) forming an aqueous suspension of nucleic acid-containing microparticles in the solvent removal device via diffusion of the organic solvent into an aqueous phase of the second emulsion. Support for independent claim 1 can be found in original claim 1 as well as in the specification at, *e.g.*, page 1, line 26, to page 2, line 9; page 4, lines 25-29; and page 33, lines 31-38.

(vi) Grounds of Rejection to be Reviewed on Appeal

I. Claims 1-4, 12-17, 19-25, 32-46, 48-50, 54, and 55 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shah, U.S. Patent No. 6,020,004 in view of Chen et al., U.S. Patent No. 6,537, 813 and Tice et al., U.S. Patent No. 4,389,330.

II. Claims 1-6, 12-17, 19-25, 32-46, 48-50, 54, and 55 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shah, U.S. Patent No. 6,020,004, taken with Chen et al., U.S. Patent No. 6,537, 813 and Tice et al., U.S. Patent No. 4,389,330 in further view of Parikh et al., U.S. Patent No. 5,660,858.

III. Claims 1-4 and 7-55 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shah, U.S. Patent No. 6,020,004, taken with Chen et al., U.S. Patent No. 6,537, 813 and Tice et al., U.S. Patent No. 4,389,330 in further view of Hartounian et al., US20020039596 and Hedley et al., U.S. Patent No. 5,783,567.

(vii) Argument

I. Rejection Under 35 U.S.C. §103(a) (Shah in view of Chen et al. and Tice et al.)

At pages 2-9 of the final Office Action, claims 1-4, 12-17, 19-25, 32-46, 48-50, 54, and 55 were rejected as unpatentable over Shah, U.S. Patent No. 6,020,004, in view of Chen et al., U.S. Patent No. 6,537, 813 ("Chen") and Tice et al., U.S. Patent No. 4,389,330 ("Tice").

(A) The Cited References do not Establish a *Prima Facie* Case of Obviousness

(i) The Combination of References would not have Resulted in the Claimed Invention

Independent claim 1 is directed to a process for preparing nucleic acid-containing microparticles. The method requires "continuous" action at the following steps (maintaining the lettering for the steps used in the claim): (b) continuously supplying a first emulsion to a mixing chamber; (c) continuously supplying a second aqueous solution to the mixing chamber; (d) continuously emulsifying the first emulsion and the second aqueous solution in the mixing chamber to form a second emulsion; and (e) continuously transferring the second emulsion from the mixing chamber to a solvent removal device. An aqueous suspension of nucleic acid-containing microparticles is ultimately formed in the solvent removal device in step (f) via diffusion of the organic solvent into an aqueous phase of the second emulsion.

Shah describes "an improved method for preparing polymeric microparticles containing an active ingredient through unique utilization of direct lyophilization of emulsion or suspension" (Shah at column 2, lines 56-59). The "direct lyophilization" methodology of Shah is used to remove aqueous and organic solvents and produce the microparticles (Shah at column 5, lines 63-65). According to Shah "[i]t is utilization of this single step, i.e., direct lyophilization of the final emulsion or suspension, which refines and simplifies the present process over previously described processes, which require multiple steps and are often cumbersome" (Shah at column 6, line 66, to column 7, line 3).

Shah differs from the method of claim 1 in that it does not describe or suggest transferring an emulsion to a solvent removal device or forming an aqueous suspension of nucleic acid-containing microparticles in a solvent removal device via diffusion of organic

solvent into an aqueous phase of the emulsion. In addition, Shah also does not describe or suggest a "continuous process" for the preparation of microparticles. Shah describes in several passages the preparation of a "continuous phase" into which a mixture of an active ingredient and a polymer are dispersed. However, Shah nowhere describes or suggests the use of a "continuous process" for the preparation of microparticles.

The final Office Action acknowledged (at page 4) that "[n]either Shah, nor Chen et al. teach removing the organic solvent from the second emulsion to form an aqueous suspension of microparticles (step 'f' of claim 1)." However, the final Office Action asserted (at page 5) that

> it would have been obvious to one of skill in the art, at the time the invention was made, to further modify the method taught by the combined teachings of Shah and Chen et al. by removing the solvent using the two-step procedure of Tice et al., with a reasonable expectation of success. The motivation to do so is provided by Tice et al., who teach that the two-step procedure results in higher levels of active agent as compared with the conventional one-step procedure.

Chen describes various methods and apparatuses for the preparation of gene therapeutic compositions as well as the compositions formed thereby. As noted above, the final Office Action acknowledged that Chen does not disclose step (f) of claim 1.

Tice does not add what is lacking in Shah and Chen and would not have led the person of ordinary skill in the art to modify the methods of Shah so as to result in the claimed invention.

Tice describes a multi-step process for the preparation of microcapsules. The "central feature" of Tice's process "resides in the fact that during preparation solvent is removed from the microcapsules suspended in a fluid medium in two distinct steps rather than in one process step" (Tice at column 2, lines 14-18). In Tice's first step, the organic solvent in the microdroplets in the organic solvent immiscible fluid is partially removed by techniques such as heating, the application of a reduced pressure, or a combination of both (Tice at column 4, lines 9-15). After Tice's first stage of solvent removal, the dispersed microcapsules in the solvent immiscible fluid medium are isolated from the fluid medium by means of separation such as decanting or filtering (Tice at column 4, lines 24-31). In Tice's second step, "the remainder of the solvent in the microcapsules is removed by extraction" (Tice at column 4, lines 32-42).

In contrast to Tice's two-step solvent removal method, step (f) of claim 1 requires that an aqueous suspension of nucleic acid-containing microparticles is formed via diffusion of the organic solvent into an aqueous phase of the second emulsion. This formation of microparticles is accomplished by removal of the solvent from nascent microparticles (via diffusion into the surrounding aqueous phase), but not necessarily from the fluid in which they are suspended (*cf.* Tice, which removes solvent in the first step of its method via evaporation). Nothing in Tice (or Shah or Chen) suggests such a means of forming nucleic acid-containing microparticles.

(ii) The Person of Ordinary Skill in the Art would not have Combined Shah and Tice

Appellants contest the assertion in the final Office Action (see passage from page 4 of the Office Action reproduced above) that the skilled person having read Shah and Tice would have had any reason to modify the single-step method of Shah to include the multi-step method of Tice.

Shah places a clear emphasis on the importance of using only a single step (i.e., direct lyophilization) on the final emulsion or suspension. The Background section of Shah refers expressly to the same Tice patent (i.e., U.S. Pat. No. 4,389,330) that is cited as a secondary reference in the present obviousness rejection. In its reference to Tice, Shah states that the solvent evaporation technique (as described in Tice) "is often not preferred because active ingredient is often lost during the solvent extraction process" (Shah at col. 2, lines 11-12). In summarizing the importance of direct lyophilization to his methods, Shah states that:

> (1) Shah's one-step method "provides several significant advantages over the processes described in the art" (Tice having been explicitly referenced as a prior art method) that include ease of manufacture of the active ingredient loaded microparticles, provision of sustained release formulations that maintain the activity and integrity of the active ingredient during release, and attainment of higher yields, high loading, and higher loading efficiencies (Shah at column 2, line 56, to column 3, line 5); and

(2) "the present process is more refined and simpler than those described in the art, and the activity and integrity of the active ingredient is maintained throughout the process" (Shah at column 3, lines 13-16).

Shah's comments on the advantages of its single-step direct lyophilization method as compared to the multi-step solvent evaporation process of Tice directly contradict the remarks in the final Office Action (at page 9) asserting that "[s]uch teachings, would motivate one of skill in the art to sacrifice simplicity for quality, i.e., to modify Shah's method by using the Tice's two-step solvent removal method." Shah clearly states that its method results in higher yields, high loading, and higher loading efficiencies. As a result, Shah teaches that its method is superior to those in the art (such as Tice) because of both (i) simplicity of manufacture, and (ii) the quality of the resulting microparticle product. Contrary to the suggestion in the final Office Action, the skilled person having read the cited references would have concluded that Shah teaches methods of preparing microparticles having all-around superior characteristics (as compared to those of Tice).

In view of the teachings of Shah and Shah's direct commentary on Tice, the skilled person would have been strongly discouraged from modifying Shah's method by adding Tice's two-step solvent removal method. Shah teaches that such a modification would have been expected to result in both a more cumbersome method as well as the production of a lower quality product. As a result, the teachings of Shah would have failed to provide the requisite reason for making the modification proposed in the final Office Action.

(B) Shah Teaches Away from the Claimed Invention

The remarks above establish that the skilled person having read Shah and Tice would have had no reason to make the modification proposed in the Office Action. In addition to the failure of the references to establish a *prima facie* case of obviousness, the comments of Shah regarding the drawbacks of Tice clearly teach away from making the Examiner's proposed modification. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant."

In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994). In this case, the skilled person would have been expressly discouraged (by the teachings of Shah) from modifying Shah's method to include Tice's two-step solvent removal method.

The final Office Action asserts (at pages 8-9) that the alleged teaching away portion of Shah "only teaches that Tice's method is not preferred for water-soluble drugs" and that "the instant case pertains to nucleic acids and not to water-soluble drugs." Appellants note that nucleic acids are water soluble and this property is well known to those of skill in the art. This fact only underscores the teaching away of Shah with respect to use of Tice's two-step solvent removal method in the preparation of nucleic acid-containing microparticles.

In view of the forgoing remarks, appellants respectfully submit that the combination of Shah, Chen, and Tice do not render obvious the claimed methods. Appellants request that the Examiner withdraw the rejection of independent claim 1 and claims 2-4, 12-17, 19-25, 32-46, 48-50, 54, and 55 that depend therefrom.

II. Rejection Under 35 U.S.C. §103(a) (Shah in view of Chen et al., Tice et al., and Parikh et al.)

At pages 9-10 of the final Office Action, claims 1-6, 12-17, 19-25, 32-46, 48-50, 54, and 55 were rejected as unpatentable over Shah taken with Chen and Tice in further view of Parikh et al., U.S. Patent No. 5,660,858 ("Parikh").

The final Office Action cited Parikh as describing the use of lipid stabilizers (recited in dependent claims 5 and 6) and asserted that "[i]t would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Shah taken with Chen et al. and Tice et al. by including lipid stabilizers".

As detailed above, the combination of Shah, Chen, and Tice does not render obvious the method of independent claim 1. Parikh provides nothing that supplements the deficiencies of Shah, Chen, and Tice or renders obvious the method of independent claim 1. Accordingly, once independent claim 1 is held allowable, all of the remaining dependent claims should also be in condition for allowance.

III. Rejection Under 35 U.S.C. §103(a) (Shah in view of Chen et al., Tice et al., Hartounian et al., and Hedley et al.)

At pages 10-12 of the final Office Action, claims 1-4 and 7-55 were rejected as unpatentable over Shah taken with Chen and Tice in further view of Hartounian et al., US20020039596 ("Hartounian") and Hedley et al., U.S. Patent No. 5,783,567 ("Hedley").

The final Office Action cited Hartounian and Hedley as allegedly describing features of various dependent claims and asserted that it would have been obvious to modify the methods of Shah, Chen, and Tice in view of Hartounian and Hedley to arrive at the methods of these dependent claims.

As detailed above, the combination of Shah, Chen, and Tice does not render obvious the method of independent claim 1. Hartounian and Hedley provide nothing that supplements the deficiencies of Shah, Chen, and Tice or renders obvious the method of independent claim 1. Accordingly, once independent claim 1 is held allowable, all of the remaining dependent claims should also be in condition for allowance.

CONCLUSION

For the reasons set forth above, appellants respectfully request that all of the rejections of claims 1-55 be reversed.

A Claims Appendix (viii) is attached and contains a copy of the claims under appeal.

An Evidence Appendix (ix) is attached as required, but contains no subject matter.

A Related Proceedings Appendix (x) is attached as required, but contains no subject matter.

The required fee in the amount of $270 is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 08191-0012002.

Respectfully submitted,

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(viii) Claims Appendix

1. A scalable continuous process for preparing nucleic acid-containing microparticles, the process comprising:

(a) providing a mixing chamber and a solvent removal device;

(b) continuously supplying a first emulsion to the mixing chamber, wherein the first emulsion comprises (i) an organic solution comprising a polymeric material and an organic solvent mixed with (ii) a first aqueous solution comprising a nucleic acid;

(c) continuously supplying a second aqueous solution to the mixing chamber, wherein the second aqueous solution comprises a surfactant;

(d) continuously emulsifying the first emulsion and the second aqueous solution in the mixing chamber to form a second emulsion, the second emulsion comprising nucleic acid, polymeric material, water, and organic solvent;

(e) continuously transferring the second emulsion from the mixing chamber to the solvent removal device; and

(f) forming an aqueous suspension of nucleic acid-containing microparticles in the solvent removal device via diffusion of the organic solvent into an aqueous phase of the second emulsion;

wherein at least one of the first emulsion and the second aqueous solution further comprises a stabilizer.

2. The process of claim 1 wherein the first aqueous solution and the second aqueous solution are of essentially equal osmolarity.

3. The process of claim 2, wherein the stabilizer comprises a carbohydrate and a buffer.

4. The process of claim 3 wherein the stabilizer comprises sucrose and TRIS-EDTA.

5. The process of claim 4 wherein the stabilizer additionally comprises a lipid.

6. The process of claim 1 wherein the stabilizer comprises a lipid.

7. The process of claim 1, further comprising:

(g) providing a diafiltration apparatus;

(h) diluting the aqueous suspension with an aqueous wash solution;

(i) supplying the diluted aqueous suspension to the diafiltration apparatus; and

(j) removing an aqueous waste solution from the diluted aqueous suspension in the diafiltration apparatus, wherein the aqueous waste solution comprises at least some of the wash solution of step (h), to form in the diafiltration apparatus a purified aqueous suspension comprising nucleic acid-containing microparticles.

8. The process of claim 7, further comprising:

(k) concentrating the purified aqueous suspension in the diafiltration apparatus to form a concentrate; and

(l) transferring the concentrate into one or more vessels.

9. The process of claim 8 further comprising:

(m) lyophilizing, freeze-drying, or air-drying the concentrate in the one or more vessels, to form lyophilized, freeze-dried, or air-dried microparticles.

10. The process of claim 9 wherein the lyophilized or freeze-dried microparticles have a residual organic solvent level of less than 200 ppm.

11. The process of claim 10 wherein the lyophilized or freeze-dried microparticles have a residual organic solvent level of less than 50 ppm.

12. The process of claim 1, further comprising:

(g) contacting the aqueous suspension with a vibrating or non-vibrating fine-mesh screen;

(h) filtering the aqueous suspension through the screen to remove at least some of each of said first and second aqueous solutions and to retain the microparticles on the screen;

(i) washing the microparticles with at least one aqueous wash solution to produce washed microparticles; and

(j) drying the washed microparticles to produce dried microparticles.

13. The process of claim 12, wherein the drying step comprises lyophilizing, freeze-drying, or air-drying the washed microparticles.

14. The process of claim 12, wherein the first aqueous wash solution is sterile water-for-injection at a temperature of about 2°C to about 8°C.

15. The process of claim 12, further comprising contacting the washed microparticles with an excipient, prior to the drying step.

16. The process of claim 12, further comprising:

(k) transferring the dried microparticles into one or more vessels.

17. The process of claim 1, wherein the mixing chamber comprises a homogenizer.

18. The process of claim 1, wherein the solvent removal device is a hardening tank.

19. The process of claim 1, wherein the second aqueous solution is supplied to the mixing chamber at a flow rate of between 0.1 and 20 l/min.

20. The process of claim 1, wherein the organic solvent is removed from the second emulsion in the solvent removal device by evaporation.

21. The process of claim 1, wherein the organic solvent is removed from the second emulsion by heating the second emulsion in the solvent removal device to between 30°C and 55°C.

22. The process of claim 1, wherein the organic solvent is removed from the second emulsion in the solvent removal device by an extraction process.

23. The process of claim 1, wherein the removal of the organic solvent from the second emulsion in the solvent removal device is facilitated by diluting the second emulsion in the solvent removal device.

24. The process of claim 1, wherein the organic solvent is removed from the second emulsion in the solvent removal device by applying a partial vacuum to the solvent removal device.

25. The process of claim 1, wherein the organic solvent comprises dichloromethane.

26. The process of claim 9, wherein each of the steps is carried out aseptically.

27. The process of claim 7, wherein the diafiltration apparatus comprises a hollow fiber system.

28. The process of claim 7, wherein steps (i) and (j) are carried out at a temperature of between about 2°C and about 8°C.

29. The process of claim 1, wherein at least about 50% of the nucleic acid in the microparticles is in the form of circular RNA molecules or supercoiled circular DNA molecules.

30. The process of claim 7, wherein at least about 50% of the nucleic acid in the microparticles in the purified aqueous suspension is in the form of circular RNA molecules or supercoiled circular DNA molecules.

31. The process of claim 9, wherein at least about 50% of the nucleic acid in the lyophilized or freeze-dried microparticles is in the form of supercoiled circular DNA molecules.

32. The process of claim 1, wherein the average diameter of microparticles is less than about 100 microns.

33. The process of claim 31, wherein the average diameter is less than about 20 microns.

34. The process of claim 32, wherein the average diameter is between about 0.5 and about 2.5 microns.

35. The process of claim 1, wherein the polymeric material is a synthetic, biodegradable polymer.

36. The process of claim 35, wherein the polymer is poly-lactic-*co*-glycolic acid (PLGA).

37. The process of claim 36, wherein the ratio of lactic acid to glycolic acid in the PLGA is between about 1:2 and about 4:1 by weight.

38. The process of claim 37, wherein the ratio of lactic acid to glycolic acid in the PLGA is about 1:1 by weight.

39. The process of claim 36, wherein the PLGA has an average molecular weight in the range of 6,000 to 100,000.

40. The process of claim 1, wherein the second aqueous solution further comprises polyvinyl alcohol (PVA).

41. The process of claim 40, wherein the second aqueous solution further comprises a carbohydrate.

42. The process of claim 41, wherein the carbohydrate is sucrose.

43. The process of claim 1, wherein the emulsifying step (d) is carried out at between about 2°C and about 8°C.

44. The process of claim 1, wherein the average residence time of the first emulsion and the second aqueous solution in the mixing chamber is less than about 60 seconds.

45. The process of claim 44, wherein the average residence time of the first emulsion and the second aqueous solution in the mixing chamber is less than about 1 second.

46. The process of claim 1, wherein the average residence time of the second emulsion in the solvent removal device is less than about 3 hours.

47. The process of claim 1, further comprising:

(g) providing a diafiltration apparatus;

(h) diluting the aqueous suspension with an aqueous wash solution;

(i) supplying the diluted aqueous suspension to the diafiltration apparatus;

(j) removing an aqueous waste solution from the diluted aqueous suspension in the diafiltration apparatus, wherein the aqueous waste solution comprises at least some of the wash solution of step (h), to form in the diafiltration apparatus a purified aqueous suspension comprising nucleic acid-containing microparticles;

(k) washing the purified aqueous suspension to form a suspension of washed microparticles;

(l) concentrating the suspension of washed microparticles to form a concentrate;

(m) transferring the concentrate into one or more vessels; and

(n) lyophilizing, freeze-drying, or air-drying the concentrate in the one or more vessels, to form lyophilized, freeze-dried, or air-dried powder.

48. The process of claim 1, wherein the first aqueous solution comprises sucrose.

49. The process of claim 1, wherein the first aqueous solution comprises EDTA.

50. The process of claim 1, wherein the first aqueous solution comprises the stabilizer.

51. The process of claim 1, wherein at least about 60% of the nucleic acid in the microparticles is in the form of circular RNA molecules or supercoiled circular DNA molecules.

52. The process of claim 1, wherein at least about 70% of the nucleic acid in the microparticles is in the form of circular RNA molecules or supercoiled circular DNA molecules.

53. The process of claim 1, wherein at least about 80% of the nucleic acid in the microparticles is in the form of circular RNA molecules or supercoiled circular DNA molecules.

54. The process of claim 1, wherein the average residence time of the first emulsion and the second aqueous solution in the mixing chamber is less than about 30 seconds.

55. The process of claim 1, wherein the average residence time of the first emulsion and the second aqueous solution in the mixing chamber is less than about 10 seconds.

(ix) Evidence Appendix

None.

(x) Related Proceedings Appendix

None.